

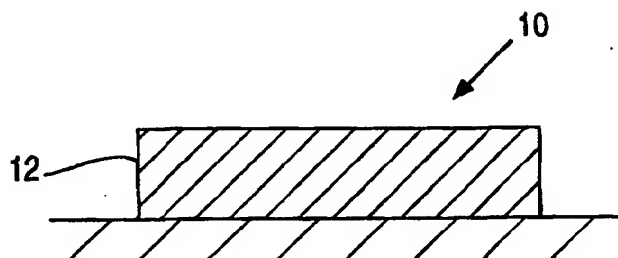


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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**(54) Title:** TRANSDERMAL DELIVERY SYSTEM USING A COMBINATION OF PERMEATION ENHANCERS**(57) Abstract**

Skin permeation enhancer compositions are provided which increase the permeability of skin to transdermally administered steroid drugs. The composition contains benzyl alcohol, propylene glycol monolaurate and a C<sub>2</sub>-C<sub>6</sub> alkanediol. The compositions are particularly useful in conjunction with the transdermal administration of progestogens and estrogens. Methods and drug delivery systems for using the enhancer compositions are provided as well.



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5        TRANSDERMAL DELIVERY SYSTEM USING A COMBINATION OF  
         PERMEATION ENHANCERS

Description

10    Technical Field

         This invention is in the field of transdermal drug delivery. More specifically it relates to methods and compositions for enhancing the permeability of the skin to steroid drugs.

15

Background

         A variety of devices and methods for administering steroid drugs transdermally have been described. The devices are generally laminated  
20    composites that include a reservoir layer that contains the drug, a pressure-sensitive adhesive layer by which the device is attached to the skin, and a backing layer that forms the outer "skin" of the device. The device may also include means for coadministering a percutaneous  
25    absorption enhancer that increases the rate of flux of the steroid drug through the skin.

         U.S. Patent No. 4,788,062 describes the transdermal administration of progesterone and an estradiol ester alone or in combination utilizing a  
30    polymer matrix and a permeation enhancer. The permeation enhancer is a surfactant or fatty acid ester and may be: sucrose monolaurate (SML), glycerol monooleate (GMO), glycerol monolaurate (GML), polyethylene glycol monolaurate (PEGML), propylene glycol laurate, propylene  
35    glycol dipelarginate and neopentyl glycol dicaprate.

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U.S. Patent No. 4,804,541 is directed to a method, composition, and article for use in transdermal or percutaneous administration of active agents, in particular, isosorbide dinitrate (ISDN), an antianginal drug, and estradiol. The active agents are dissolved in benzyl alcohol. The benzyl alcohol promotes cutaneous absorption while enhancing percutaneous delivery.

U.S. Patent No. 4,911,916 is directed to a device and a diffusion matrix for transdermal drug administration. The diffusion matrix useful as a reservoir for the drug is a viscoelastic body of (a) a reticulated polymeric foam framework; (b) a viscoelastic drug-permeable hydrophobic polymer embedded in the pores of the foam; (c) a drug dispersed in and at least partly dissolved in the hydrophobic polymer; and optionally (d) an agent dispersed in and at least partly dissolved in the hydrophobic polymer that enhances the solubility of the drug in the polymer and/or is a percutaneous absorption enhancer that increases the permeability of skin to the drug. The permeability of the skin to estradiol may be enhanced with the following compounds: fatty acid esters, fatty alcohol ethers of C<sub>2</sub> to C<sub>4</sub> alkanediols, where each fatty acid/alcohol portion of the ester/ether is of about 8 to 22 carbon atoms and is straight or branched chain, preferably straight chain, is saturated or has 1 to 3 sites of olefinic unsaturation and has 0 to 2 hydroxyl groups, are phase compatible with the preferred type of hydrophobic polymer, and increase the solubility of estradiol in such polymer. Monoesters and monoethers of straight chain alkanediols whose hydroxyl groups are on terminal carbon atoms are preferred, especially propylene glycol monolaurate (PGML).

U.S. Patent No. 4,913,905 describes a transdermal therapeutic system for the combined

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administration of estrogen and a synthetic gestagen. The estrogen and gestagen are in combination with an agent that enhances percutaneous absorption, increasing the flux of the combination through the skin. Suitable penetration enhancers are noted to be monovalent, saturated or unsaturated aliphatic, cycloaliphatic or aromatic alcohols having from 4 to 12 carbon atoms, e.g. hexane, cyclohexane, isopropylbenzene, cycloaliphatic aromatic aldehydes and ketones having from 4 to 10 carbon atoms, such as cyclohexanone, acetamide, N,N-di-lower alkylacetamides such as N,N-dimethylacetamide or N,N-diethylacetamide, C<sub>10</sub>-C<sub>20</sub>-alkanoylamides, e.g. N,N-dimethyl-lauroylamide, 1-n-C<sub>10</sub>-C<sub>20</sub>-alkylazacycloheptan-2-one, e.g. 1-n-dodecylazacycloheptan-2-one, or N-2-hydroxyethylacetamide, and known vehicles and/or penetration enhancers such as aliphatic, cycloaliphatic and aromatic esters, N,N-di-lower alkylsulphoxides, unsaturated oils, halogenated or nitrated aliphatic or cycloaliphatic hydrocarbons, salicylates, polyalkylene glycol silicates and mixtures thereof. C<sub>2</sub>-C<sub>4</sub> alkanol, e.g. isopropanol or isobutanol and especially ethanol are preferred.

U.S. Patent No. 5,023,084 describes a estrogen/progestin transdermal dosage unit. Permeation enhancers for the active agents are described and include saturated and unsaturated fatty acids and their ester alcohols, monoglycerides, acetate, diethanolamides and N,N-dimethylamides, preferably n-decyl alcohol or capric acid.

U.S. Patent No. 5,053,227 describes skin permeation enhancer compositions for the delivery of active agents, particularly steroids, transdermally. The permeation enhancer compositions include a first component that is either a diethylene glycol monoethyl ether or a diethylene glycol monomethyl ether, and a

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second component that is an ester of the formula  
 $[\text{CH}_3(\text{CH}_2)_m\text{COO}]_n\text{R}$  where m is 8 to 16, n is 1 or 2, and R  
is a lower alkyl residue.

It has now been determined that the particular  
5 combination of permeation enhancers of the present  
invention allows for the simultaneous delivery of a high  
flux of a progestogen and a low flux of a potent estrogen  
through the human skin.

#### 10 Disclosure of the Invention

In one aspect, this invention is a skin  
permeation enhancer composition for use in the  
transdermal delivery of a steroid drug. The skin  
permeation enhancer composition includes benzyl alcohol,  
15 propylene glycol monolaurate (PGML) and a  $\text{C}_2\text{-C}_6$   
alkanediol.

In another aspect, the invention is a method  
and transdermal delivery system for steroid drugs that  
include a skin permeation enhancer composed of benzyl  
20 alcohol, propylene glycol monolaurate and a 1-6 carbon  
alkanediol.

#### Brief Description of the Drawings

Figs. 1 and 2 are schematic drawings of  
25 representative matrix systems of the invention.

#### Modes for Carrying Out the Invention

"Penetration enhancement" or "permeation  
enhancement" as used herein relates to an increase in the  
30 permeability of skin to a pharmacologically active agent,  
i.e. so as to increase the rate at which the drug  
permeates through the skin and enters the bloodstream.

"Carriers" or "vehicles" refer to carrier  
materials suitable for transdermal drug administration  
35 and include any such material known in the art, e.g. any

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liquid, gel, solvent, liquid diluent, solubilizer or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable carriers include water, mineral oil, silicone, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials. In addition, one or both of the components or the enhancer composition may also serve as a carrier.

As used herein, "matrix-type" denotes a device in which the drug reservoir is a solid matrix of a homogeneous mixture of drug and a pressure-sensitive adhesive. Typically one surface of the matrix will define the basal surface (i.e., that surface which contacts the skin and forms a diffusional pathway for the drug to migrate from the device to the skin) of the device. Additional reservoir layers may be included in the device. These devices are intended to deliver drugs for a period of between about 2 days and 2 weeks, preferably about 7 days.

The term "transdermal" is intended to denote transport through skin or mucosa such as the buccal mucosa.

The term "therapeutically effective amount" denotes that dose of drug that will provide the pharmacological effect for which the drug is indicated.

The term "potent" intends drugs that are therapeutically effective at doses below about 200  $\mu\text{g/day}$ , more typically below about 100  $\mu\text{g/day}$ . Examples of such drugs are ethinyl estradiol, gestodine, mestranol, 3-keto-desogestrol, levonorgestrel and norgestimate. These drugs may be administered singly or in combination depending upon the condition being treated. For instance, combinations of estrogens or combinations of estrogens and progestogens may be administered to provide hormone replacement therapy or

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for contraceptive purposes. Examples of drugs that would be considered to be "non-potent" drugs in that they are therapeutically effective at doses above 200  $\mu\text{g/day}$ , usually above 300  $\mu\text{g/day}$  and typically between about 300  
5 and 1000  $\mu\text{g/day}$  include norethindrone, norethindrone acetate and estradiol and its esters.

The term "skin flux" intends the rate of drug transmitted through skin per unit time as determined by the procedure described in PCT/US90/04767. For hormone  
10 replacement or contraceptive therapy, the desired flux of norethindrone acetate will normally be between about 0.3 and 3.0  $\mu\text{g/cm}^2/\text{hr}$ , preferably about 0.5 to 2.0  $\mu\text{g/cm}^2/\text{hr}$ . For a potent estrogen, the desired flux in hormone replacement or contraceptive therapy will normally be  
15 0.02 to 0.10  $\mu\text{g/cm}^2/\text{hr}$ , preferably about 0.05 to 0.07  $\mu\text{g/cm}^2/\text{hr}$ .

The present invention involves the use of a novel permeation enhancer composition for the transdermal delivery of a steroid drug composition. Examples of  
20 steroid drugs that can be delivered include: progestogens such as norethindrone, norethindrone acetate, desogestrel, 3-keto desogestrel, gestadene, levonorgestrel and norgestimate; estrogens such as estradiol and its esters, e.g. estradiol valerate, cyprionate, decanoate and acetate, as well as ethinyl  
25 estradiol; corticosteroids such as cortisone, hydrocortisone, fluocinolone acetonide; and testosterone. The steroid drug composition may include one or more steroid drugs. In a particular embodiment, the steroid drug composition includes a progestogen and an estrogen.  
30 One example of such steroid drug composition is norethindrone acetate and ethinyl estradiol. In this example, the targeted delivery rate of the norethindrone acetate is between about 300 and 1000  $\mu\text{g/day}$ , preferably  
35 between about 500 to 900  $\mu\text{g/day}$  and the targeted delivery



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rate of ethinyl estradiol is between about 20 and 50  $\mu\text{g/day}$ , preferably about 30 to 40  $\mu\text{g/day}$ .

The permeation enhancement composition of the present invention may in addition include one or more  
5 selected carriers or excipients, and various agents and ingredients commonly employed in dermatological ointments and lotions. For example, fragrances, opacifiers, preservatives, anti-oxidants, gelling agents, perfumes, thickening agents, stabilizers, surfactants, emollients,  
10 coloring agents, and the like may be incorporated.

The method of delivery of the present compositions may vary but necessarily involves applying the selected composition to a defined surface of the skin or other tissue for a period of time sufficient to  
15 provide the desired blood level of drug for the desired period of time. The method may involve direct application of the composition as an ointment, gel cream, or the like or may involve use of drug delivery devices as taught, for example in the following United States  
20 Patents: No. 3,742,951, No. 3,797,494 and No. 4,568,343.

A transdermal delivery system can be constructed with the enhancer composition described for sustained delivery of steroid drugs. The targeted skin flux can be achieved by adjusting vehicle composition and  
25 vehicle loading, as well as by adjusting the surface area through which the compositions are administered. In the Examples described below, the matrix-type systems are constructed according to the method described in PCT/US90/04767. The drug delivery systems contain one or  
30 more drug/permeation enhancer reservoirs, a backing layer, and optionally one or more additional layers as are known to those of skill in the art of transdermal drug delivery.

The drug reservoir layer or layers are  
35 formulated so as to contain the selected steroid or

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steroids as well as the enhancer composition. The polymeric matrix layers may contain up to about 10 wt% of steroid drug (e.g. 0-5 wt% estrogen and 0-5 wt% progestogen), up to about 50 wt% permeation enhancer composition (e.g. 1-10 wt% benzyl alcohol, 1-10 wt% PGML and 0-30 wt% alkanediol). The polymeric material which serves as the reservoir for this mixture is typically a pressure sensitive adhesive such as polyisobutylene, low density polyethylene, silicone, acrylate adhesive or other suitable rubber or polymeric materials. The layers may be formulated so that the steroid drug or drugs are below saturation, at saturation, or above saturation.

A combination of estrogen and progestogen may be delivered simultaneously using a single matrix-type delivery system. The drugs and permeation enhancers are included in the silicone adhesive layer. Drug flux is controlled by the amount of drug that is loaded into this layer. Where both drugs are non-potent steroids, a high flux of both estrogen and progestogen can be achieved by incorporating both steroids into the adhesive layer above saturation. Where it is desirable to have a high flux of the progestogen and a low flux of an estrogen such as where the progestogen is a non-potent steroid and the estrogen is a potent steroid, the adhesive layer will be loaded with the estrogen at a concentration below saturation and the progestogen at or above saturation.

A combination of estrogen and progestogen may also be delivered simultaneously using a matrix-type system that contains at least one additional drug reservoir layer. In such case, low flux of a potent drug may be achieved by incorporating the potent drug into a low diffusivity matrix such as one made of polyisobutylene (PIB), PIB with polyethylene, polyacrylate or other suitable low diffusivity polymer matrix, that is where the diffusion coefficient of the

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drug in the polymer is below about  $1 \times 10^{-8}$  cm<sup>2</sup>/sec, preferably between about  $1 \times 10^{-10}$  and  $1 \times 10^{-8}$  cm<sup>2</sup>/sec, while the progestogen and enhancer combination is incorporated into the silicone adhesive layer. Examples  
5 of such potent drug may be a potent estrogen such as ethinyl estradiol and the non-potent drug may be a progestogen such as norethindrone acetate.

The backing membrane, which may be either occlusive or nonocclusive, is preferably comprised of a  
10 flexible, stretchable, polymer film, e.g., polyether urethane, polyester urethane, polyamide, or other related copolymers. The material and thickness selected for the backing membrane is preferably such that a transdermal system can be provided having good wearability for at  
15 least a seven-day application but is usually in the range of 0.5 to 5 mils.

The area of the basal surface of the skin through which drug is transmitted by diffusion will typically be in the range of 10 to 50 cm<sup>2</sup>, typically  
20 between about 25 and 35 cm<sup>2</sup>. The particular area will be correlated with the skin flux to provide the requisite daily drug dose to provide therapy.

As will be established in the Examples which follow, the combination of enhancers may be used to  
25 increase the skin flux of a non-potent drug (i.e. a progestogen such as norethindrone acetate) while maintaining the skin flux of a potent drug (i.e. a potent estrogen such as ethinyl estradiol) at a fairly low level. Additionally, different delivery profiles of the  
30 drugs can be obtained by adjusting the drug loading of the drugs. Said another way, one can obtain, for example, a higher non-potent progestogen flux with a higher progestogen loading and a lower potent estrogen flux with a lower estrogen loading. Additionally, by  
35 including the permeation enhancer composition of the

- 10 -

present invention, recrystallization of the steroid drugs is avoided and high drug loading (above saturation) is obtainable. Further, the enhancer combination improves the tack and cohesive strength of the high vehicle loaded  
5 silicone adhesive.

The following Examples further illustrate this invention. These examples are not intended to limit the invention in any manner.

Examples

10

### Example 1

The single layer matrix system (10) shown in Figure 1 was prepared and the following formulations included:

- 15 (A) (1) 2% norethindrone acetate  
(2) 0.2% ethinyl estradiol  
(3) 5% benzyl alcohol  
(4) 6% PGML  
(5) 20% 1,4-butanediol

- 20 (B) (1) 2% norethindrone acetate  
(2) 0.1% ethinyl estradiol  
(3) 5% benzyl alcohol  
(4) 6% PGML  
25 (5) 15% 1,5-pentanediol

33.2% of Formula (A) and 66.8% of Silicone adhesive and 29.1% of Formula (B) and 70.9% Silicone adhesive were each blended together in a 250 ml container for 1 hour at room temperature. Each blend was cast into a 50 micron thick Melinex 442/200 polyester backing and dried in an oven at 70°C. The resulting composites (12) were designed to exhibit an in vitro skin flux of 0.8-2.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  of norethindrone acetate and 0.1-0.4  $\mu\text{g}/\text{cm}^2/\text{hr}$  of ethinyl estradiol over 7 days.

35 of ethinyl estradiol over 7 days.

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Skin flux tests were carried out on these composites as described in PCT/US90/04767. In each case, as shown in Table 1, below, the flux of norethindrone acetate is between 1.0 and 1.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  and the flux of ethinyl is between 0.1 and 0.3  $\mu\text{g}/\text{cm}^2/\text{hr}$ . The lower drug loading of ethinyl estradiol in Formula (B) (0.1% vs. 0.2% in Formula (A)) leads to a lower skin flux of the ethinyl estradiol.

10

Table 1

FORMULATION	FLUX ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )	
	Norethindrone Acetate	Ethinyl Estradiol
15 Formula (A)	1.03 $\pm$ 0.07	0.29 $\pm$ 0.02
Formula (B)	1.28 $\pm$ 0.13	0.18 $\pm$ 0.02

Example 2

20 The double layer matrix system (20) shown in Figure 2 was prepared and the following formulations included:

(A) In a silicone layer:

- 25 (1) 2% norethindrone acetate  
(2) 5% benzyl alcohol  
(3) 6% PGML  
(4) 15% 1,5-pentanediol

In a polyisobutylene layer:

- 30 (5) 1% ethinyl estradiol

(B) In a silicone layer:

- 35 (1) 2% norethindrone acetate  
(2) 5% benzyl alcohol  
(3) 6% PGML

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(4) 15% 1,5-pentanediol

In a low density (60:40) polyethylene/  
polyisobutylene layer:

5 (5) 1% ethinyl estradiol

28% Formula (A) (1)-(4) and 72% Silicone adhesive and 28%  
Formula (B) (1)-(4) and 72% Silicone adhesive were each  
blended together in a 250 ml container for 1 hour at room  
10 temperature. 1% Formula A(5) and 99% of a  
polyisobutylene adhesive and 1% Formula B(5) and 99% of a  
60:40 ratio of low density polyethylene/polyisobutylene  
were blended together in a 250 ml container for 1 hour at  
room temperature. The Formula (A) blends and Formula (B)  
15 blends were each cast into a 50 micron thick Melinex  
442/200 polyester backing and dried in an oven at 70°C.  
The resulting laminated composites comprising an ethinyl  
estradiol layer (22) and a norethindrone acetate layer  
(24) were designed to exhibit an in vitro skin flux of  
20 0.8-2.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  of norethindrone acetate and 0.1-0.4  
 $\mu\text{g}/\text{cm}^2/\text{hr}$  of ethinyl estradiol over 7 days. In each  
case, as shown in Table 2, below, the flux of  
norethindrone acetate is between 1.0 and 1.3  $\mu\text{g}/\text{cm}^2/\text{hr}$   
and the flux of ethinyl is between 0.1 and 0.3  $\mu\text{g}/\text{cm}^2/\text{hr}$ .

25

Table 2

FORMULATION	FLUX ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )	
	Norethindrone Acetate	Ethinyl Estradiol
30 Formula (A)	1.22 $\pm$ 0.04	0.16 $\pm$ 0.03
Formula (B)	1.05 $\pm$ 0.17	0.10 $\pm$ 0.01

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Modifications of the above described modes for carrying out the invention that are obvious to those of skill in the fields of pharmaceuticals, transdermal drug delivery, and related fields are intended to be within  
5 the scope of the following claims.

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Claims

We claim:

1. A transdermal delivery system for administering a therapeutically effective amount of a steroid drug to a patient comprising:
  - (a) a steroid drug; and
  - (b) a permeation enhancer composition comprising a benzyl alcohol, propylene glycol monolaurate and a C<sub>2</sub>-C<sub>6</sub> alkanediol.
2. The system of claim 1 wherein the C<sub>2</sub>-C<sub>6</sub> alkanediol is selected from the group consisting of 1,5-pentanediol, 1,3-butanediol, 1,4-butanediol and 2,3-butanediol.
3. The system of claim 2 wherein the C<sub>2</sub>-C<sub>6</sub> alkanediol is 1,5-pentanediol.
4. The system of claim 1 wherein the steroid drug comprises a progestogen, an estrogen or a mixture thereof.
5. The system of claim 4 wherein the steroid drug comprises a mixture of an estrogen and a progestogen.
6. The system of claim 5 wherein the estrogen is a potent estrogen and the progestogen is a non-potent progestogen.
7. The system of claim 6 wherein the progestogen is norethindrone or norethindrone acetate, and the estrogen ethinyl estradiol.



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8. The system of claim 5 wherein the estrogen and progestogen are potent steroids.

9. The system of claim 5 wherein the estrogen  
5 and progestogen are non-potent steroids.

10. A transdermal delivery system for administering a therapeutically effective amount of a steroid drug to a patient comprising:

10 a drug reservoir comprising a polymeric adhesive matrix;  
a backing layer laminated thereto, comprising a flexible polymer film; and  
contained within the reservoir, a steroid drug  
15 and a permeation enhancer composition comprising a benzyl alcohol, propylene glycol monolaurate and a C<sub>2</sub>-C<sub>6</sub> alkanediol.

11. A transdermal delivery system for  
20 administering a therapeutically effective amount of a steroid drug to a patient comprising:

a first drug reservoir comprising a polymeric adhesive matrix;  
a second drug reservoir comprising a low  
25 diffusivity polymeric matrix;  
a backing layer laminated thereto, comprising a flexible polymer film; and  
contained within the first reservoir, a steroid drug and a permeation enhancer composition comprising a  
30 benzyl alcohol, propylene glycol monolaurate and a C<sub>2</sub>-C<sub>6</sub> alkanediol and contained within the second reservoir, a second, potent steroid drug.

12. A method for enhancing the flux of a  
35 steroid drug through the skin, comprising transdermally

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administering the drug in combination with a permeation enhancing amount of a composition comprising:

- (a) benzyl alcohol;
- (b) propylene glycol monolaurate; and
- 5 (c) a C<sub>2</sub>-C<sub>6</sub> alkanediol.

13. The method of claim 12 wherein the C<sub>2</sub>-C<sub>6</sub> alkanediol is selected from the group consisting of 1,5-pentanediol, 1,3-butanediol, 1,4-butanediol and 2,3-  
10 butanediol.

14. The method of claim 13 wherein the C<sub>2</sub>-C<sub>6</sub> alkanediol is 1,5-pentanediol.

15 15. The method of claim 12 wherein the steroid drug comprises a progestogen, an estrogen or a mixture thereof.

16. The method claim 15 wherein the steroid  
20 drug comprises a mixture of a progestogen and an estrogen.

17. The method of claim 16 wherein the  
25 estrogen is a potent estrogen and the progestogen is a non-potent progestogen.

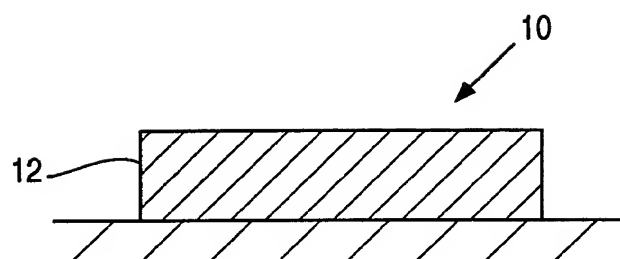
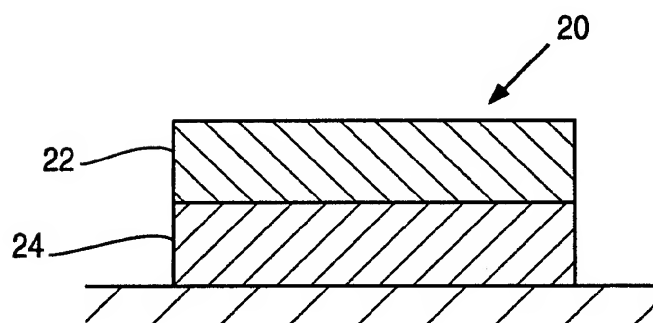
18. The method of claim 17 wherein the  
progestogen is norethindrone or norethindrone acetate,  
and the estrogen ethinyl estradiol.

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19. The method of claim 16 wherein the  
estrogen and progestogen are potent steroids.

20. The method claim 16 wherein the estrogen  
35 and progestogen are non-potent steroids.

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**FIG. 1****FIG. 2**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/08636

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61F 13/00

US CL : 424/559

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449, 448; 514/946, 947

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,053,227 (CHIANG ET AL) 01 October 1991, see column 6, line 56 through column 7, line 35; claims 1-8.	1-20
Y	US, A, 4,804,541 (NICHOLS) 14 February 1989, see claims 1 and 3.	1-20
Y	US, A, 4,552,872 (COOPER ET AL) 12 November 1985, see column 6, lines 63-64 and column 8, lines 56-62.	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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